FELODIPINE TRANSDERMAL DEVICE AND METHODS

This application claims the benefit of U.S. Provisional Application No. 60/242,514, Filed October 23, 2000, which is hereby incorporated by reference.

Background of the Invention

It is the intent of all sustained-release pharmaceutical preparations to provide a longer period of pharmacologic effect after the administration of a drug than is ordinarily experienced after the administration of immediate release preparations of the same drug. Such longer periods of efficacy can provide many inherent therapeutic benefits that are not achieved with corresponding immediate release preparations. The benefits of prolonged treatment of hypertension (high blood pressure) afforded by sustained release oral preparations have become universally recognized and oral sustained-release preparations are commercially available.

Another approach to sustained delivery of a therapeutically active agent is transdermal delivery systems, such as transdermal patches. Generally, transdermal patches contain a therapeutically active agent, a reservoir or matrix containing the active ingredient(s) and an adhesive which allows the transdermal device to adhere to the skin, allowing for the passage of the active agent from the device through the skin of the patient. Once the active agent has penetrated the skin layer, the drug is absorbed into the blood stream where it can exert a desired pharmacotherapeutic effect.

Transdermal delivery of antihypertensives, such as felodipine, have been contemplated. For example, U.S. Patent No. 5,834,496 issued November 10, 1998 to Young, hereby incorporated by reference, relates to methods and compositions utilizing the optical pure (-S) isomer of felodipine for treating conditions such as hypertension, angina, cerebral ischemia, cerebral disorders, arrhythmias, cardiac hypertrophy, coronary vasospasm, myocardial infarction, renal impairment and acute renal failure.

Felodipine, commercially available as Plendil® in the U.S. from AstraZeneca Pharmaceuticals LP (Wilmington, DE 15437, U.S.A.), is a calcium antagonist (calcium channel blocker). Specifically, felopine is a dihydropyridine derivative with the chemical name, 4-(2,3-dichlorophenyl)-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate, and it is used in the treatment of hypertension. It is a racemic mixture, and it is in the form of a

slightly yellowish powder that is not soluble in water but freely soluble in dichloromethane and ethanol. Felodipine causes a decrease in the intracellular concentration of calcium ions, which leads to a reduction in blood pressure. The recommended starting oral dosage of felodipine is 5 mg once daily, and depending on the response of the patient can be increased up to 10 mg daily or decreased to 2.5mg daily. In elderly patients or patients with liver or renal problems, the initial oral dosage felodopine should be 2.5 mg daily with the dosage being adjustable as set forth above.

High blood pressure or hypertension occurs when the blood exerts excessive force upon the walls of the arteries. Blood pressure is measured as two numbers; systolic (pressure of the blood in the arteries when the heart beats) and diastolic (pressure when the heart is at rest between heartbeats). A normal blood pressure is consider to be around 120 (systolic)/80 (diastolic) mm Hg, whereas a reading of about 140 (systolic)/90 (diastolic) mm Hg or higher is considered to be high blood pressure. High blood pressure causes the heart to work extra hard, which in turn eventually leads to an enlarged heart, putting the individual at increased risk of having a heart attack or stroke. Some possible causes of high blood pressure include thinning of the arteries, increased heart rate, increased volume of blood, excitement, and nervousness.

Symptoms of hypertension are improved by treatment with a group of antihypertensives known as calcium channel antagonists (calcium channel blockers). Calcium channel antagonists such as felodipine (The Merck Index, 11th Edition, Merck & Co., Inc., Rahway, N.J. U.S.A. 1989, hereby incorporated by reference) inhibit the influx of extracellular calcium across the membranes of the myocardial and vascular smooth muscle cells, causing the blood vessels to relax, and thereby reducing blood pressure. (Goodman and Gillmans, The Pharmacological Basis of Therapeutics, 9th Edition, hereby incorporated by reference). Felodipine has a greater selectively for vascular smooth muscle than for cardiac muscle.

Following oral administration, felodipine is rapidly absorbed and undergoes extensive first pass metabolism, resulting in a bioavailibility of approximately 20 percent. Pharmacokinetic studies have revealed that the onset of antihypertensive activity occurs within 2-5 hours following administration of felodipine. Mean peak concentrations are reached in 2.5-5 hours after administration. The mean elimination half-life is roughly 11 to 16

hours. Metabolism of felodopine results in its excretion in the urine (70%) and the feces (10%). Felodipine is 99% plasma-protein bound.

The most common adverse side effects of felopidine are peripheral edema and headaches. Other side effects include chest infection, dizziness, palpitations, diarrhea, constipation, flushing, rash, fatigue, and gingival enlargement (Physicians' Desk Reference, 53rd Edition, 1999, hereby incorporated by reference).

Despite advances in the art, there remains a need for methods of treating patients with hypertension with an agent that provides effective levels of felodipine for prolonged periods of time while eliminating or minimizing the symptoms of hypertension, and the above mentioned side effects, thus providing a safe and effective method of management of this condition.

Objects and Summary of the Invention

It is an object of the present invention to provide a continuous plasma felodipine concentration in mammals, preferably human patients suffering from hypertension.

It is an object of the present invention to provide a method for treating patients suffering from hypertension with a transdermal delivery system, which achieves prolonged and effective management of this condition, while at the same time provides the opportunity to reduce possible side effects, e.g., which patients may experience when subjected to prolonged oral therapy.

It is another object to provide a method for the treatment of hypertension in patients by utilizing a transdermal delivery system, which contains felodipine.

In certain embodiments, the present invention is directed to a method of effectively treating hypertension, angina, or both conditions in a human patient, comprising administering felodipine transdermally to the human patient by applying a transdermal delivery system containing felodipine to the skin of a patient, and maintaining the transdermal delivery system in contact with the skin of the patient for at least 3 days, the transdermal delivery system maintaining an effective mean relative release rate to provide a therapeutic blood level of the felodipine within 36 hours from the initiation of the dosing

interval, and thereafter maintaining a therapeutic blood level until the end of at least the three-day dosing interval.

In certain embodiments, the present invention is directed to a method of effectively treating hypertension, angina, or both conditions in a human patient, comprising administering felodipine transdermally to the human patient by applying a transdermal delivery system containing felodipine to the skin of a patient, and maintaining the transdermal delivery system in contact with the skin of the patient for at least 5 days, the transdermal delivery system maintaining an effective mean relative release rate to provide a therapeutic blood level of the felodipine within three days from the initiation of the dosing interval, and thereafter maintaining a therapeutic blood level until the end of at least the five-day dosing interval.

In certain embodiments, the present invention is directed to a method of lessening the incidence of side-effects in a patient associated with the oral administration of felodipine, wherein the method comprises administering the felodipine in a transdermal delivery system over at least twenty-four hours and thereby lessening the incidence of side effects.

In certain embodiments, the above methods can further comprise providing a mean relative release rate of felodipine from the transdermal delivery system to provide a plasma level of felodipine of at least about 0.1 ng/ml within about 6 hours, 3 hours, 2 hours, 1 hour or 0.5 hours after application of the transdermal delivery system onto the skin of the patient.

In certain embodiments, the above methods can further comprise providing a felodipine transdermal delivery system, which maintains a plasma level of felodipine at steady-state from about 1.0 to about 3.0 ng/ml or from about 1.5 to about 2.3 ng/ml.

In certain embodiments, the above methods can further comprise maintaining a therapeutic plasma level from about 0.1 ng/ml to about 3.3 ng/ml during the dosing interval for the transdermal delivery system.

In certain embodiments, the above methods can further comprise having the transdermal delivery system have a mean relative release rate from about 0.5 μm/hour/cm^2 to about 25 μm/hour/cm2, from about 1 μm/hour/cm^2 to about 20 μm/hour/cm^2, or from about 2

μm/hour/cm^2 to about 10 μm/hour/cm^2.

In certain embodiments, the above methods can further comprise having the transdermal delivery system have a mean relative release rate from about 4.2 μg/cm^2/hr to about 20.0 μg/cm^2/hr at 24 hours; from about 3.3 μg/cm^2/hr to about 14.0 μg/cm^2/hr at 48 hours; and from about 2.7 μg/cm^2/hr to about 10.8 μg/cm^2/hr at 72 hours; as determined via an in-vitro permeation test utilizing a Valia-Chien cell where the membrane is a human cadaver skin and the cell has a receptor chamber containing a 40:60 mixture of Ethanol:water.

In certain embodiments, the above methods can further comprise having the transdermal delivery system provide an in-vitro cumulative amount of permeation of from about 63 μg/cm^2 to about 388 μg/cm^2 at 24 hours; from about 105 μg/cm^2 to about 660 μg/cm^2 at 48 hours; and from about 139 μg/cm^2 to about 854 μg/cm^2 at 72 hours, as determined via an in-vitro permeation test utilizing a Valia-Chien cell where the membrane is a human cadaver skin and the cell has a receptor chamber containing a 40:60 mixture of Ethanol:water.

In certain embodiments, the above methods can further comprise having the plasma level of felodipine at 48 hours after administration not decrease by more than 30% over the next 72 hours.

In certain embodiments, the above methods can further comprise maintaining an effective mean relative release rate of the transdermal delivery system to provide a substantially first order plasma level increase of felodipine from the initiation of the dosing interval until about 48 to about 72 hours after the initiation of the dosing interval; and thereafter providing an effective mean relative release rate to provide a substantially zero order plasma level fluctuation of felodipine until the end of at least the five-day dosing interval.

In certain embodiments, the above methods can further comprise administering the felodipine in a transdermal delivery system applied to the skin of a human patient for about 3 to about 5 days.

In certain embodiments, the invention is directed to a transdermal delivery system containing felodipine or a pharmaceutically acceptable salt thereof which provides a mean relative release rate from about 0.5 μm/hour/cm^2 to about 25 μm/hour/cm^2, from about 1 μm/hour/cm^2 to about 20 μm/hour/cm^2, or from about 2 μm/hour/cm^2 to about 10 μm/hour/cm^2 of the transdermal delivery system; a plasma level of felodipine of at least about 0.1 ng/ml by about 6 hours after application of the transdermal delivery system onto the skin of the patient; and a plasma level of felodipine at steady-state from about 0.1 to about 3.3 ng/ml.

In certain embodiments, the invention is directed to a transdermal delivery system which provides a mean relative release rate from about 4.2 μg/cm^2/hr to about 20.0 μg/cm^2/hr at 24 hours; from about 3.3 μg/cm^2/hr to about 14.0 μg/cm^2/hr at 48 hours; and from about 2.7 μg/cm^2/hr to about 10.8 μg/cm^2/hr at 72 hours; as determined via an in-vitro permeation test utilizing a Valia-Chien cell where the membrane is a human cadaver skin and the cell has a receptor chamber containing a 40:60 mixture of Ethanol:water.

In certain embodiments, the invention is directed to a transdermal delivery system which provides an in-vitro cumulative amount of permeation of from about 63 μg/cm^2 to about 388 μg/cm^2 at 24 hours; from about 105 μg/cm^2 to about 660 μg/cm^2 at 48 hours; and from about 139 μg/cm^2 to about 854 μg/cm^2 at 72 hours; and from about 231 μg/cm^2 to about 850 μg/cm^2 at 96 hours; as determined via an in-vitro permeation test utilizing a Valia-Chien cell where the membrane is a human cadaver skin and the cell has a receptor chamber containing a 40:60 mixture of Ethanol:water.

In certain embodiments, the transdermal delivery system maintains a plasma level of felodipine at steady-state from about 1.0 to about 3.0 ng/ml or from about 1.5 to about 2.3 ng/ml.

In certain embodiments, the transdermal delivery system maintains an effective mean relative release rate to provide a therapeutic blood level of the felodipine within three days from the initiation of the dosing interval, and thereafter maintaining a therapeutic blood level until the end of at least the five-day dosing interval.

In certain embodiments, the transdermal delivery system provides a mean relative release rate of felodipine effective to provide a plasma level of felodipine of at least about 0.1 ng/ml by about 6 hours, 3 hours, 2 hours, 1 hour or 0.5 hours after application of the transdermal delivery system onto the skin of the patient.

In certain embodiments, the transdermal delivery system maintains a therapeutic plasma level from about 0.1 ng/ml to about 3.3 ng/ml during the dosing interval for the transdermal delivery system.

In certain embodiments, the transdermal delivery system provides a mean relative release rate from about 0.5 μg/hour/cm^2 to about 25 μg/hour/cm^2, from about 1 μm/hour/cm^2 to about 20 μm/hour/cm^2, or from about 2 μm/hour/cm^2 to about 10 μm/hour/cm^2 of the transdermal delivery system.

In certain embodiments, the transdermal delivery system provides a mean relative release rate from about 4.2 μg/cm^2/hr to about 20.0 μg/cm^2/hr at 24 hours; from about 3.3 μg/cm^2/hr to about 14.0 μg/cm^2/hr at 48 hours; and from about 2.7 μg/cm^2/hr to about 10.8 μg/cm^2/hr at 72 hours; and a mean relative release rate from about 2.4 μg/cm^2/hr to about 8.9 μg/cm^2/hr at 96 hours; as determined via an in-vitro permeation test utilizing a Valia-Chien cell where the membrane is a human cadaver skin and the cell has a receptor chamber containing a 40:60 mixture of Ethanol:water.

In certain embodiments, the transdermal delivery system provides an in-vitro cumulative amount of permeation of from about 63 μg/cm^2 to about 388 μg/cm^2 at 24 hours; from about 105 μg/cm^2 to about 660 μg/cm^2 at 48 hours; and from about 139 μg/cm^2 to about 854 μg/cm^2 at 72 hours; and from about 231 μg/cm^2 to about 850 μg/cm^2 at 96 hours; as determined via an in-vitro permeation test utilizing a Valia-Chien cell where the membrane is a human cadaver skin and the cell has a receptor chamber containing a 40:60 mixture of Ethanol:water.

It is another object to provide a transdermal device containing felodipine, which provides effective blood plasma levels of felodipine when the device is applied to the skin of a mammal, preferably a human.

It is another object of the invention to provide a transdermal device containing felodipine, which provides effective treatment of hypertension in patients.

It is yet a further object to provide a transdermal device containing felodipine and a method for the treatment of hypertension in patients which maximizes the dosage interval, i.e., the interval during which the transdermal delivery system is maintained in contact with the skin, and minimizes the plasma concentrations and or fluctuations in plasma concentrations in the patients during the dosage interval, while surprisingly maintaining effective management of hypertension.

It is yet a further object to provide transdermal delivery device comprising felodipine or a pharmaceutically acceptable salt thereof which maintains an effective mean relative release rate to provide a therapeutic blood level of the felodipine within three days from the initiation of the dosing interval, and thereafter maintaining a therapeutic blood level until the end of at least the five-day dosing interval.

It is yet a further object to provide a method for lessening the peripheral edema and headaches with the oral administration of felodipine.

In accordance with the above objects and others, the present invention is directed in part to a transdermal device for achieving the above methods.

In further embodiments, the invention is directed to a transdermal device and method which, when applied to the skin of a mammal such as a human patient, provides therapeutically effective blood plasma levels of felodipine to effectively treat hypertension in a human patient, wherein the transdermal device is maintained in contact with the patient's skin for at least 5 days, the transdermal delivery system maintaining an effective mean relative release rate to provide a therapeutic blood level of the felodipine within three days from the initiation of the dosing interval, and thereafter maintaining a therapeutic blood level until the end of at least the five-day dosing interval.

The invention is further directed to a transdermal felodipine device for the effective treatment of hypertension, which device, when applied to the skin of a patient maintained in contact with the patient's skin for at least 3 days, has an effective mean relative release rate to

provide a therapeutic blood level of the felodipine within 36 hours from the initiation of the dosing interval, and thereafter maintains a therapeutic blood level until the end of at least the three-day dosing interval.

The invention is further directed in part to a transdermal felodipine device for the treatment of hypertension, which provides substantially zero order pharmacokinetics over a significant portion of the dosage interval.

The invention is further directed to a transdermal device and a method of effectively treating hypertension in a human patient, comprising applying the transdermal felodipine device to the skin of the patient and maintaining the transdermal delivery system in contact with the skin of a patient for at least 5 days, the transdermal delivery system maintaining an effective mean relative release rate to provide a substantially first order plasma level increase of felodipine from the initiation of the dosing interval until about 48 to about 72 hours after the initiation of the dosing interval; and thereafter providing an effective mean relative release rate to provide a substantially zero order plasma level fluctuation of felodipine until the end of at least the five-day dosing interval.

The invention is further directed to a transdermal felodipine device which when applied to the skin of a patient and maintained in contact with the patient's skin for at least 3 days, has an effective mean relative release rate to provide a substantially first order plasma level increase of felodipine from the initiation of the dosing interval until about 24 hours after the initiation of the dosing interval; and thereafter provides an effective mean relative release rate to provide a substantially zero order plasma level fluctuation of felodipine until the end of at least the three-day dosing interval.

The invention is further directed to a transdermal felodipine device and a method for lessening the incidence of side-effects in a patient associated with the oral administration of felodipine, wherein the method comprises administering the felodipine in a transdermal dosage form over at least twenty-four hours and thereby lessening the incidence of side effects.

The invention is further directed to a transdermal felodipine device and method which provides for reduced side-effects and avoids peak plasma concentrations of felodipine in a patient associated with the oral administration of felodipine (i.e., reduces the peak plasma level relative to immediate release orally delivered felodipine), via the administration of felodipine in a transdermal dosage form over at least twenty-four hours, thereby lessening the incidence of side effects and avoiding the peak plasma concentrations of felodipine.

It is yet a further object to provide a transdermal delivery system suitable for the above methods.

For example, the above methods can be achieved utilizing a transdermal therapeutic system for the administration of felodipine to the skin comprising a backing layer which is impermeable to the active substance, a pressure-sensitive adhesive reservoir layer, and optionally a removable protective layer, the reservoir layer by weight comprising 20 to 90% of a polymeric matrix, 0.1 to 30% of a softening agent, 0.1 to 20% of felodipine base or of a pharmaceutically acceptable salt thereof and 0.1 to 30% of a solvent for the felodipine or salt thereof.

Another alternative is to utilize a laminated composite for administering felodipine or a pharmaceutically acceptable salt thereof to an individual transdermally comprising (a) a polymer backing layer that is substantially impermeable to felodipine or the pharmaceutically acceptable salt thereof; and
(b) a reservoir layer comprising an acrylate or silicon based pressure-sensitive adhesive, 0.1 to 20% of felodipine base or of a pharmaceutically acceptable salt thereof, 0.1 to 30% of an ester of a carboxylic acid acting as a softening agent and 0.1 to 30% of a solvent for felodipine having at least one acidic group.

The methods of the present invention are described in further detail in the following sections. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention pertains. However, it should be understood that for purposes of the present invention, the following terms have the following meanings:

The term "effective treatment of hypertension" is defined for purposes of the present invention as a satisfactory reduction in or elimination of the symptoms associated with hypertension, along with the process of a tolerable level of side effects, as determined by the human patient.

Drug release from membrane-controlled systems may be defined as follows:

Amount released per area unit Q = const (zero order kinetics)

The term "mean relative release rate" is determined from the amount of drug released per unit time from the transdermal delivery system through the skin and into the bloodstream of a human patient. Mean relative release rate may be expressed, e.g., as $\mu g/cm^2/hr$. For purposes of the invention, it is understood that relative release rates may change between any particular time points within a particular dosing interval, and the term therefore only reflects the overall release rate during the particular dosing interval.

For purposes of the present invention, relative release rate should be considered synonymous with the term "flux rate".

The term "sustained release" is defined for purposes of the present invention as the release of the drug (felodipine) from the transdermal formulation at such a rate that blood (e.g., plasma) concentrations (levels) are maintained within the therapeutic range (above the minimum effective concentration) but below toxic levels over a period of time of about 3 days or longer.

The term "steady state" means that the blood plasma concentration curve for a given drug has been substantially repeated from dose to dose.

The term "minimum effective concentration" is defined for purposes of this invention as the minimum effective therapeutic blood plasma level of the drug at which at least some therapeutic effect in treating hypertension is achieved in a given patient.

The term "overage" means for the purposes of the present invention the amount of felodipine contained in a transdermal delivery system, which is not delivered to the patient. The overage is necessary for creating a concentration gradient by means of which the active

agent (e.g., felodipine) migrates through the layers of the transdermal dosage form to the desired site on a patient's skin.

The term "first order" pharmacokinetics is defined as plasma concentrations, which increase over a specified time period.

The term "zero order" pharmacokinetics contemplates an amount of drug released from a felodipine formulation, which substantially maintains plasma concentrations at a relatively constant level. For purposes of the present invention, a relatively constant plasma concentration is defined as a concentration, which does not decrease more than about 30% over a 48 hour time period.

Drug release from membrane-controlled systems may be defined as follows:

Amount released per area unit $Q = const$ (zero order kinetics)

The term "mean relative release rate" is determined from the amount of drug released per unit time from the transdermal delivery system through the skin and into the bloodstream of a human patient. Mean relative release rate may be expressed, e.g, as $\mu g/cm^2/hr$. For example, a transdermal delivery system that releases 10 mg of felodipine over a time period of 24 hours is considered to have a relative release rate of $4.1 \times 10^{-4} \mu g/hr$. For purposes of the invention, it is understood that relative release rates may change between any particular time points within a particular dosing interval, and the term therefore only reflects the overall release rate during the particular dosing interval. For purposes of the present invention, relative release rate should be considered synonymous with the term "flux rate".

The term "sustained release" is defined for purposes of the present invention as the release of the drug from the transdermal formulation at such a rate that blood (e.g., plasma) concentrations (levels) are maintained within the therapeutic range (above the minimum effective drug concentration or "MEDC") but below toxic levels over a period of time of about 3 days or longer.

The term "steady state" means that the blood plasma concentration curve for a given drug has been substantially repeated from dose to dose.

The term "minimum effective concentration" is defined for purposes of this invention as the minimum effective therapeutic blood plasma level of the drug at which at least some therapeutic effect in treating hypertension is achieved in a given patient.

For purposes of the present invention, the term "felodipine" shall include felodipine base, pharmaceutically acceptable salts thereof, stereoisomers thereof, enantiomers thereof, ethers thereof, and mixtures thereof.

For purposes of this invention, the terms "transdermal delivery system" and "transdermal device" are interchangeable.

BRIEF DESCRIPTION OF THE DRAWINGS

The following drawings are illustrative of embodiments of the invention and are not meant to limit the scope of the invention as encompassed by the claims.

FIG. 1 is a graphical representation of the average cumulative amount of felodipine resulting from 4 permeation tests of Example 1 through human cadaver skin.

FIG. 2 is a graphical representation of the average felodipine permeation rate (flux rate) of Example 1 through human cadaver skin.

FIG. 3 is a graphical representation of the average cumulative amounts of felodipine resulting from permeation tests of Examples 2 and 4 through human cadaver skin.

FIG. 4 is a graphical representation of the average felodipine permeation rates (flux rates) of Examples 2 and 4 through human cadaver skin.

FIG. 5 is a graphical representation of the average cumulative amounts of felodipine resulting from permeation tests of Examples 3 and 5 through human cadaver skin.

FIG. 6 is a graphical representation of the average felodipine permeation rates (flux rates) of Examples 3 and 5 through human cadaver skin.

FIG. 7 is a graphical representation is a graphical representation of the cumulative amounts of felodipine resulting from 3 permeation tests of Example 6 through human cadaver skin.

FIG. 8 is a graphical representation of the average felodipine permeation rate (flux rate) of Example 6 through human cadaver skin.

FIG. 9 is a graphical representation of the average cumulative amounts of felodipine resulting from permeation tests of Examples 7, 8 and 9 through human cadaver skin.

FIG. 10 is a graphical representation of the average felodipine permeation rates (flux rates) of Examples 7, 8 and 9 through human cadaver skin.

FIG. 11 is a graphical representation of the average cumulative amounts of felodipine resulting from the permeation tests of Examples 7 and 10 through human cadaver skin.

FIG. 12 is a graphical representation of the average cumulative amounts of felodipine resulting from the permeation tests of Examples 7 and 11 through human cadaver skin.

FIG. 13 is a graphical representation of the cumulative amounts of felodipine resulting from 3 permeation tests of Example 12 through human cadaver skin.

FIG. 14 is a graphical representation of the average permeation rate (flux rate) of felodipine resulting from 3 permeation tests of Example 12 through human cadaver skin.

FIG. 15 is a graphical representation of the average cumulative amount of felodipine resulting from 3 permeation tests of Example 13 through human cadaver skin.

FIG. 16 is a graphical representation of the average felodipine permeation rate (flux rate) of Example 13 through human cadaver skin.

Detailed Description

Transdermal delivery of active agents is measured in terms of "relative release rate" or "flux", i.e., the rate of penetration of the active agent through the skin of an individual. Skin flux may be generally determined from the following equation:

$$dm/dT=J=P * C$$

where J is the skin flux, P is the permeability coefficient and C is the concentration gradient across the membrane, assumed to be the same as the donor concentration. m represents the amount of drug entering the blood stream. The variable dm/dT represent the change in amount of drug entering the blood stream and change over time.

It is well understood in the art of transdermal delivery systems that in order to maintain a desired flux rate for a desired dosing period, it is necessary to include an overage of active agent in the transdermal delivery system in an amount that is substantially greater than the amount to be delivered to the patient over the desired time period. For example, to maintain the desired flux rate for a three day time period, it is considered necessary to include much greater than 100% of a three-day dose of an active agent in a transdermal delivery system. This overage is necessary for creating a concentration gradient by means of which the active agent migrates through the layers of the transdermal delivery system to the desired site on a patient's skin. The remainder of the active agent remains in the transdermal delivery system. It is only the portion of active agent that exits the transdermal delivery system that becomes available for absorption into the skin. The total amount of active agent absorbed into the patient's blood stream is less than the total amount available. The amount of overage to be included in a transdermal delivery system is dependent on these and other factors known to the skilled artisan.

It has been found that it is possible to treat hypertension according to the present invention by providing a transdermal delivery system containing a sufficient amount of felodipine to provide a desired relative release rate for at least about 3 days, and after single administration (application) of the transdermal dosage form, leaving the dosage form on the skin for approximately a 3 to 8 day time period, thereby resulting in the flux being maintained over the prolonged period and effective blood plasma levels and management of hypertension being maintained over the prolonged period. Preferably, the desired flux is maintained at least about 5, preferably at least about 7 days after application of the

transdermal delivery system.

Transdermal dosage forms used in accordance with the invention preferably include a backing layer made of pharmaceutically acceptable material, which is impermeable to felodipine. The backing layer preferably serves as a protective cover for the active agent, e.g. felodipine and may also provide a support function. Examples of materials suitable for making the backing layer are films of high and low density polyethylene, polypropylene, polyvinylchloride, polyurethane, polyesters such as poly(ethylene terephthalate), metal foils, metal foil laminates of such suitable polymer films, textile fabrics, if the components of the reservoir cannot penetrate the fabric due to their physical properties and the like. Preferably, the materials used for the backing layer are laminates of such polymer films with a metal foil such as aluminum foil. The backing layer can be any appropriate thickness, which will provide the desired protective and support functions. A suitable thickness will be from about 10 to about 200 microns. Desirable materials and thickness will be apparent to the skilled artisan.

Matrix Systems

In certain preferred embodiments, the transdermal dosage forms used in accordance with the invention contain a polymer matrix layer. Generally, the polymers used to form the biologically acceptable polymer matrix are those capable of forming thin walls or coatings through which pharmaceuticals can pass at a controlled rate. A non-limiting list of exemplary materials for inclusion in the polymer matrix includes polyethylene, polypropylene, ethylene/propylene copolymers, ethylene/ethylacrylate copolymers, ethylene vinyl acetate copolymers, silicones, rubber, rubber-like synthetic homo-, co- or block polymers, polyacrylic esters and the copolymers thereof, polyurethanes, polyisobutylene, chlorinated polyethylene, polyvinylchloride, vinyl chloride-vinyl acetate copolymer, polymethacrylate polymer (hydrogel), polyvinylidene chloride, poly(ethylene terephthalate), ethylene-vinyl alcohol copolymer, ethylene-vinyloxyethanol copolymer, silicones including silicone copolymers such as polysiloxane-polymethacrylate copolymers, cellulose polymers (e.g., ethyl cellulose, and cellulose esters), polycarbonates, polytetrafluoroethylene and mixtures thereof.

Preferred materials for inclusion in the polymer matrix layer are silicone elastomers of the general polydimethylsiloxane structures, (e.g., silicone polymers). Preferred silicone polymers cross-link and are pharmaceutically acceptable. Other preferred materials for inclusion in the polymer matrix layer include: silicone polymers that are cross-linkable copolymers having dimethyl and/or dimethylvinyl siloxane units which can be crosslinked using a suitable peroxide catalyst. Also preferred are those polymers consisting of block copolymers based on styrene and 1,3-dienes (particularly linear styrene-isoprene-block copolymers of styrene-butadiene-block copolymers), polyisobutylenes, polymers based on acrylate and/or methacrylate.

The polymer matrix layer may optionally include a pharmaceutically acceptable cross-linking agent. Suitable crosslinking agents include, e.g., tetrapropoxy silane.

Preferred transdermal delivery systems used in accordance with the methods of the present invention include an adhesive layer to affix the dosage form to the skin of the patient for a desired period of administration, e.g., about 3 to about 8 days. If the adhesive layer of the dosage form fails to provide adhesion for the desired period of time, it is possible to maintain contact between the dosage form with the skin by, for instance, affixing the dosage form to the skin of the patient with an adhesive tape, e.g, surgical tape. It is not critical for purposes of the present invention whether adhesion of the dosage form to the skin of the patient is achieved solely by the adhesive layer of the dosage form or in connection with a peripheral adhesive source, such as surgical tape, provided that the dosage form is adhered to the patient's skin for the requisite administration period.

The adhesive layer preferably includes using any adhesive known in the art that is pharmaceutically compatible with the dosage form and preferably hypoallergenic, such as polyacrylic adhesive polymers, acrylate copolymers (e.g., polyacrylate) and polyisobutylene adhesive polymers. In other preferred embodiments of the invention, the adhesive is a pressure-sensitive contact adhesive, which is preferably hypoallergenic.

The transdermal dosage forms, which can be used in accordance with the present invention, may optionally include a permeation-enhancing agent. Permeation enhancing agents are compounds, which promote penetration and/or absorption of the felodipine into the blood stream of the patient. A non-limiting list of permeation enhancing agents includes

polyethylene glycols, surfactants, and the like.

Alternatively, permeation of felodipine may be enhanced by occlusion of the dosage form after application to the desired site on the patient with, e.g. an occlusive bandage. Permeation may also be enhanced by removing hair from the application site by, e.g. clipping, shaving or use of a depilatory agent. Another permeation enhancer is heat. It is thought that heat enhancement can be induced by, among other things, using a radiating heat form, such as an infrared lamp, onto the application site after application of the transdermal dosage form. Other means of enhancing permeation of felodipine such as the use of iontophoretic means are also contemplated to be within the scope of the present invention.

A preferred transdermal dosage form which may be used in accordance with the present invention includes a non-permeable backing layer made, for example, of polyester; an adhesive layer made, for example of a polyacrylate; and a matrix containing the felodipine and other desirable pharmaceutical aids such as softeners, permeability enhancers, viscosity agents and the like.

The active agent may be included in the device in a drug reservoir, drug matrix or drug/adhesive layer. Preferably, the active agent is felodipine or a pharmaceutically acceptable salt thereof.

Certain preferred transdermal delivery systems also include a softening agent. Suitable softening agents include higher alcohols such as dodecanol, undecanol, octanol, esters of carboxylic acids, wherein the alcohol component may also be a polyethoxylated alcohol, diesters of dicarboxylic acids, such as di-n-butyladiapate, and triglycerides particularly medium-chain triglycerides of the caprylic/capric acids or coconut oil, have proved to be particularly suitable. Further examples of suitable softeners are multivalent alcohols, for example, levulinic acid, cocprylic acids glycerol and 1,2-propanediol, which can also be etherified by polyethylene glycols.

A felodipine solvent may also be included in the transdermal delivery systems of the present invention. Preferably, the solvents dissolve the felodipine to a sufficient extent thereby avoiding complete salt formation. A non-limiting list of suitable solvents include those with at least one acidic group. Particularly suitable are monoesters of dicarboxylic acids

such as monomethylglutarate and monomethyladipate.

Other pharmaceutically acceptable compounds which may be included in the reservoir or matrix include: solvents, for example alcohols such as isopropanol; permeation enhancing agents such as those described above; and viscosity agents, such as cellulose derivatives, natural or synthetic gums, such as guar gum, and the like.

In preferred embodiments, the transdermal dosage form includes a removable protective layer. The removable protective layer is removed prior to application, and consists of the materials used for the production of the backing layer described above provided that they are rendered removable, for example, by a silicone treatment. Other removable protective layers, for example, are polyltetra-fluoroethylene, treated paper, allophane, polyvinyl chloride, and the like. Generally, the removable protective layer is in contact with the adhesive layer and provides a convenient means of maintaining the integrity of the adhesive layer until the desired time of application.

The composition of the transdermal dosage forms used in accordance with the invention and the type of device used are not considered critical to the method of the invention, provided that the device delivers the active agent, e.g. felodipine, for the desired time period and at the desired flux rate and/or the desired delivery rate of the transdermal dosage form.

Certain transdermal dosage forms for use in accordance with the present invention are described in U.S. Patent No. 5,240,711 (Hille, *et. al.;* assigned to LTS Lohmann Therapie-Systeme GmbH & Co.), hereby incorporated by reference. Such transdermal delivery systems may be a laminated composite having an impermeable backing layer containing felodipine, e.g., instead of buprenorphine, and optionally a permeation enhancer combined with a pressure-sensitive adhesive. A preferred transdermal dosage form in accordance with the '711 patent includes: (i) a polyester backing layer which is impermeable to the drug; (ii) a polyacrylate adhesive layer; (iii) a separating polyester layer; and (iv) a matrix containing felodipine, a solvent for the felodipine, a softener and a polyacrylate adhesive. The felodipine solvent may or may not be present in the final formulation. The transdermal delivery device described therein includes a backing layer, which is impermeable to the active substance, a pressure-sensitive adhesive reservoir layer, and optionally, a removable protective layer.

Preferably, the reservoir layer includes about 10 to about 95%-wt polymeric material, about 0.1 to about 40%-wt softener, about 0.1 to about 30%-wt felodipine. A solvent for the felodipine base or pharmaceutically acceptable salt thereof may be included as about 0.1 to about 30%-wt.

The transdermal delivery system may also be prepared in accordance with the disclosure of International Patent Application No. WO 96/19975 (Hille, *et. al.;* assigned to LTS Lohmann Therapie-Systeme GMBH), hereby incorporated by reference, where felodipine is substituted for buprenorphine as an active agent. In this device, the felodipine transdermal delivery device contains resorption-promoting auxiliary substances. The resorption-promoting auxiliary substance forms an under cooled mass. The delivery system contains 10% felodipine base, 10-15% acid (such as levulinic acid), about 10% softener (such as oleyoleate); 55-70% polyacrylate; and 0-10% polyvinylpyrollidone (PVP).

Reservoir Devices

Alternatively, the transdermal device may be a reservoir system. A reservoir system transdermal drug delivery patch comprises several different components. An exemplary construction includes a backing layer, an active drug and optional permeation enhancing solvent gel, a membrane, a skin contact adhesive layer, and a protective release coated liner film. Characteristics of each component are set forth below:

Backing Film: This layer is exposed to the external environment when the system is worn on the skin surface. It is impervious to penetration of the active drug contained within the system preventing the escape of the active drug through the backing film. The backing film serves as barrier layer. Moisture, soaps, lotions and other elements are prevented from entering the system and diluting the active ingredients or altering the release characteristics of the system. The active drug and solvent are contained within the system to perform its designated function. The backing film also forms one half of the chamber, which contains the active drug reservoir. The backing film must be capable of being suitably attached to the membrane in order to form the reservoir chamber. Typical attachment methods include thermal, ultrasonic polymer heat seal or welding, and adhesive bonding. Necessary mechanical properties include a low compliance for conformability to the skin surface and elasticity to allow for movement with the skin surface. Typical thickness is in the range of 0.5 – 25.0 mil. Wide ranges of homogenous, woven, and non-woven polymer or

composite materials are suitable as backing films.

Membrane: The membrane in combination with the backing film forms the chamber, which contains the active drug reservoir. The membrane is attached to the backing film, and provides a support surface for the skin contact adhesive. The membrane can be a homogenous polymer film, or a material with a porous structure. The membrane may also be designed to control the transport rate of the active drug and/or the permeation enhancing solvent. Necessary mechanical properties include a low compliance for conformability to the skin surface and elasticity to allow for movement with the skin surface. Typical thickness is in the range of 0.25 – 30.0 mil (1 mil = 0.001 inch), and more preferably in the range of 0.5 to 25.0 mil. Wide ranges of homogenous, porous, woven, and non-woven polymer or composite materials are suitable as membranes and known in the art.

Active Drug Reservoir: The active drug is combined with a liquid vehicle to fill the reservoir chamber. A range of solvents can be used for the liquid vehicle. The solvents can be chosen to optimize skin permeation of the active (enhancers) or to optimize the permeation characteristics of the membrane or the adhesion of the skin contact adhesive. A viscosity-increasing agent is often included in the vehicle to aide in the handling and system manufacturing process. The composition of the vehicle must be compatible with the other components of the system. The vehicle may be in the form of a solution, suspension, cream, lotion, gel, physical mixture or emulsion. This list is not meant to be exhaustive.

Skin Contact Adhesive: The system is affixed to the skin with a skin contact adhesive. The adhesive may cover the entire surface of the system membrane, be applied in an intermittent pattern, or only to the perimeter of the system. The adhesive composition must be of materials suitable for skin contact without creating intolerable adverse effects such as excessive skin irritation or sensitization. Adequate adhesion to the membrane and skin are also necessary. The adhesive must also possess enough cohesive integrity to remain completely on the membrane upon removal of the system. The adhesive is applied in a thickness to provide a weight of 0.025 to 50.0 mg/cm^2, more preferably 0.25 to 5.0 mg/cm^2 and most preferably 0.3 to 0.6 mg/cm^2. Typical materials include silicone, polyisobutylene (PIB), and acrylates dissolved in organic solvents, aqueous emulsions, or directly applied by hot melt processing.

Release Coated Liner Film: The liner film is removed from the system before application to the skin surface. The liner film serves the function as a protective barrier to the skin contact adhesive prior to use. The coating on the liner provides a release capability for the adhesive, allowing separation of the liner from the adhesive. A coating is not necessary if the liner material is readily removed from the adhesive without disrupting the reservoir system. Typical thickness is in the range of 0.5 – 25.0 mil. A wide range of homogenous, woven, and non-woven paper, polymer or composite materials are suitable as liner films. Release coatings are typically composed of paraffin, polyethylene, silicone or fluorocarbons.

In other embodiments, the transdermal delivery system may be a plaster such as that described in U.S. Patent No. 5,225,199 to Hidaka *et al.*, hereby incorporated by reference. Such plasters include a film layer including a polyester film of about 0.5 to about 4.9 μm thickness, about 8 to about 85 g/mm strength, respectively in the two directions intersecting substantially at right angles, about 30 to about 150% elongation, in the two directions intersecting substantially at right angles and an elongation ratio of A to B of about 1.0 to about 5.0, wherein A and B represent data in two directions intersecting at right angles, and A is greater than B and wherein said polyester film includes about 0.01 to about 1.0% by weight, based on the total weight of the polyester film, of solid fine particles in which the average particle size is about 0.001 to about 3.0 μm and an adhesive layer which is composed of an adhesive containing transdermally absorbable drugs; wherein the adhesive layer is laminated on said film layer over the surface in about 2 to about 60 μm thickness. The average particle size is substantially not more than 1.5 times the thickness of the polyester film.

The transdermal delivery system used in the present invention may also be prepared in accordance with U.S. Patent No. 5,879,701, issued March 9, 1999 to Audett, *et al.*, hereby incorporated by reference, wherein solubilization enhancer compositions are provided which facilitate transdermal administration of basic drugs from transdermal systems composed of nonpolar adhesive materials. The solubilization enhancing composition is particularly useful in facilitating the administration of basic drugs using transdermal systems worn for at least four days containing drug reservoirs comprised of nonpolar materials such as polyisobutylene adhesives or the like. The solubilizing enhancing composition itself is preferably a liquid, which is an isomeric acid mixture. Examples of suitable solubilizers include, but are not

limited to, oleic acid dimer and neodecanoic acid, with oleic acid dimer particularly preferred. The solubilizer constitutes at least about 0.10 wt.% of the reservoir, and preferably represents on the order of 0.25 wt.% to 1.0 wt.% of the reservoir. The amount of enhancer composition present in the drug formulation will depend on a number of factors, e.g., the strength of the particular enhancer composition, the desired increase in skin permeability, and the amount of drug, which is necessary to deliver.

The pharmacokinetic information for felodipine is available in the literature. The adult oral dosage for felodipine is 10 mg/day. The bioavailability for the drug is approximately 20%, expressed as fraction, 0.20 of the oral dose made available to the blood stream from gastrointestinal absorption. A release rate for a felodipine transdermal delivery system was calculated from this data. 0.20 of the oral 10 mg daily dose provides 2.0 mg of felodipine available into the blood stream. Therefore, an equal dose is required to be delivered transdermally. 2.0 mg/day is converted to 2000 mcg/24 hours. This would require delivery of 83.3 mcg/hour. The largest desirable surface area for a transdermal patch is about 40 cm^2. Dividing 83.3 mcg/hour/40 cm^2 by 40, yields a release rate of 2.1 mcg/hour/cm^2 of transdermal patch surface area. To account for drug elimination, further pharmacokinetic data and physiological data were required. The plasma concentration at steady state for felodipine is 0.002 mcg/ml. The physiological clearance rate is 48,000 ml/hour. The dosing rate is obtained from the product of the steady state concentration of felodipine and a representative clearance rate. This product is 96 mcg/hour. The largest desirable surface area for a transdermal patch is about 40 cm^2. Dividing 96 mcg/hour/40 cm^2 by 40, yields a release rate of 2.4 mcg/hour/cm^2 of transdermal patch surface area. One of skill would expect a larger input rate or flux to maintain a steady state concentration in consideration of the loss of drug in the plasma due to elimination. A confirmatory calculation for flux requires further pharmacokinetic parameters. The volume of distribution for felodipine is 700,000 ml and the half-life is 14 hours. The elimination rate constant is 0.693/half-life. The product of steady state concentration, volume of distribution and steady state concentration yields a rate of 69.3 mcg/hour. The largest desirable surface area for a transdermal patch is about 40 cm^2. Dividing 69.3 mcg/hour/40 cm^2 by 40, yields a release rate of 1.73 mcg/hour/cm^2 of transdermal patch surface area.

Any type of transdermal delivery system may be used in accordance with the methods of the present invention so long as the desired pharmacokinetic and pharmacodynamic response(s) are attained over at least 3 days, e.g., from about 5 to about 8 days. Preferable transdermal delivery systems include e.g., transdermal patches, transdermal plasters, transdermal discs, iontophoretic transdermal devices and the like.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The following examples illustrate various aspects of the present invention. They are not to be construed to limit the claims in any manner whatsoever.

Overview of Method of Manufacture: Matrix System

The following general method is used in the following examples in which the transdermal device tested is a matrix system (device):

Step 1: Preparation of the active drug vehicle/solvent/adhesive matrix. Active drug is combined with the liquid vehicle components and the adhesive components using appropriate mixing techniques well known in the art. Simple mechanical mixers, motionless mixers, homogenizers, high shear mixers, and magnetic mixing devices can be employed.

Step 2: Preparation of the active drug/adhesive matrix coated liner. Active drug/adhesive matrix coating is done with continuous web based equipment on a commercial scale. Small sheet batches can be made readily in the lab manually. A mechanism for applying a controlled thickness coating of the active drug/adhesive matrix onto the liner is employed. If solvent-based adhesives are used, a procedure for driving off the solvent and drying the active drug/adhesive matrix is employed. The open surface of the active drug/adhesive matrix on the liner must be protected during processing. A second intermediate liner can be used to cover this active drug/adhesive matrix surface.

Step 3: Laminating of the membrane to active drug/adhesive and/or liner. The membrane is typically applied on line after solvent removal on a commercial scale. This avoids the need for a second liner. A separate web and a heat and/or pressure lamination station bonds the two layers. The membrane provides a non-stick surface to the open side of the adhesive and allows for further processing in a roll form.

Overview of the Manufacture of Reservoir Devices

The following general method is used in the following examples in which the transdermal device tested is a reservoir system (device):

Step 1: Preparation of the adhesive coated liner. Adhesive coating is done with continuous web based equipment on a commercial scale. Small sheet batches can be made readily in the lab manually. A mechanism for applying a controlled thickness coating of the adhesive onto the liner is employed. If solvent-based adhesives are used, a procedure for driving off the solvent and drying the adhesive is employed. The open surface of the adhesive on the liner must be protected during processing. A second intermediate liner can be used to cover this adhesive surface.

Step 2: Laminating of the membrane to adhesive and/or liner. The membrane is typically applied on line after solvent removal on a commercial scale. This avoids the need for a second liner. A separate web and a heat and/or pressure lamination station bonds the two layers. The membrane provides a non-stick surface to the open side of the adhesive and allows for further processing in a roll form.

Step 3: Preparation of the active vehicle/solvent combination. Active drug is combined with the liquid vehicle components using appropriate mixing techniques well known in the art. Simple mechanical mixers, motionless mixers, homogenizers, high shear mixers, and magnetic mixing devices can be employed. Other ingredients are also incorporated at this time. These may include permeation enhancers and viscosity thickeners, for example.

Step 4: Finalizing the delivery system utilizing the form, fill and seal process incorporating the reservoir and backing film. This process can be carried out in either a horizontal or vertical plane. The horizontal mode requires a thickened viscosity of the reservoir vehicle, while the vertical mode can handle liquid vehicles of minimal viscosity. In the horizontal mode a dispensing head places a fixed volume drop of the drug vehicle onto the surface of the membrane. The backing film is then placed over the drop of vehicle, and then bound to the membrane to enclose the active/vehicle. A heated die is commonly used to form a heat seal welded bond. In web based systems a die cutting and packaging station often follows.

In-Vitro Skin Permeation Test Method

The test methods utilized in the following examples involve the use of a permeation cell. Several permeation cell designs are available for in-vitro permeation testing. These include "Franz cells", "Valia-Chien cells", and "Bronaugh cells". Each cell design shares several common characteristics. All cells are made with a definable surface area for permeation. All cells contain two chambers and a clamping mechanism to hold the test membrane positioned between the two cell chambers. Several exemplary test membranes include mouse skin and human cadaver skin. The membrane may be oriented in either the horizontal or vertical plane based on the cell special arrangement. One chamber serves as a reservoir (donor) for the drug to be tested; the second is a place where the permeated drug is accumulated (receptor). The receptor is often chosen to mimic the physiological conditions found beneath the membrane in-vivo. In the case where a complete transdermal system is the donor, it is clamped between the two chambers and only the receptor chamber is filled.

Calculation of the permeation rate (J) requires knowledge of the concentration (C) of the drug in the receptor chamber, the permeation area (A), sampling interval (t) and the receptor volume (V). The equation below is typical:

$J = CV / At$ where: J = micrograms/cm^2-hr

C = micrograms/ml

V = ml

$A = cm^2$

t = hr

Only the drug concentration and testing time vary in typical experiments. The drug concentration is determined by any appropriate analytical technique such as high performance liquid chromatograpy, gas chromatograpy, column elusion, or ultraviolet spectrophotometry. Other considerations in the testing system may include temperature control systems, receptor stirring systems, flow through receptor chambers, and automated sampling equipment utilizing pumps and fraction collectors. Partial receptor sampling protocols have been used in situations where the sensitivity of the analytical method for determining the drug concentration was less than optimal.

Sample testing protocols for felodipine follow.

Cells	Valia Chien
Membrane	Human cadaver skin
A (cm2)	0.636
V (ml)	4.0
receptor	Ethanol/water 40/60
sampling points	6, 24, 48, 72, 120, 144, 168 hours
sampling mode:	partial, 0.6ml per point, replace with fresh receptor.

HPLC conditions for determination of drug concentration.

Column	Hypersil C18, 5μm, 4.6mm x 25cm
Mobile phase	Acetonitrile/Buffer 70/30
Buffer:	0.01M phosphate @ pH 4.5
Flow rate	1 ml/min
UV detection	237 nm
Injection volume	20 microl
Retention time	5.0 min

EXAMPLE 1

A Felodipine reservoir and adhesive formulation was prepared having the formulation set forth in Table 1A below:

TABLE 1A

Ingredient	Amount (gm)
Felodipine	1.0
Ethanol	22.0
Water	27.0
Total	50.0
Polyethylene membrane	
Silicone adhesive	

The formulation of Example 1 was prepared and incorporated into a permeation testing apparatus according to the following procedure:

1. Felodipine is dissolved with ethanol and water and the solution is placed into the donor cell.
2. The polyethylene membrane is coated with a silicone adhesive and placed against the donor cell. The adhesive coated membrane is positioned opposite from the donor cell.
3. Thereafter, the human cadaver skin is placed between the adhesive coated polyethylene membrane and the receptor cell and the apparatus is secured.

The formulation of Example 1 was tested using a permeation cell with definable surface area for permeation. The receptor of the permeation cell was Ethanol:water (40:60) and the test substrate through which transdermal delivery was sought was human cadaver skin. Samples of 1.0 ml were taken at time intervals set out in Table 1B. These samples were tested for felodipine concentration using high performance liquid chromatography (HPLC). The HPLC conditions for determination of drug concentration are set forth below:

HPLC conditions for determination of felodipine concentration.

Column	Hypersil C18, 5µm, 4.6mm x 25cm
Mobile phase	Acetonitrile/Buffer 70/30
Buffer:	0.01M phosphate @ pH 4.5
Flow rate	1 ml/min
UV detection	237 nm
Injection volume	20 microl
Retention time	5.0 min

Four replicate tests were conducted as in Example 1 (1-1, 1-2, 1-3, 1-4) giving the results listed in Table 1B below:

TABLE 1B

	$\mu g/cm^2$					
Hours	**Test 1-1**	**Test 1-2**	**Test 1-3**	**Test 1-4**	**Average of all 4 tests**	**Std Dev**
5	16.611	12.946	18.032	15.448	15.759	2.153
20	135.630	117.674	128.331	112.386	123.505	10.455
24	175.266	152.028	163.546	144.055	158.724	13.625
29	217.579	188.997	203.093	179.139	197.202	16.768
44	350.066	293.706	316.102	286.074	311.487	28.703
48	391.569	325.124	349.833	319.258	346.446	32.870
53	435.926	359.183	386.294	354.876	384.070	37.263
68	561.320	456.850	493.185	462.905	493.585	47.885
72	600.145	485.137	524.621	495.586	526.372	51.941
77	642.980	515.838	559.107	531.361	562.322	58.673
94	777.340	614.863	668.878	647.212	677.073	70.433
120	990.946	769.437	837.548	836.397	858.582	93.811
144	1190.839	908.827	985.583	995.354	1020.151	120.190
168	1385.558	1042.131	1124.715	1145.671	1174.519	147.622

Based on the permeation results of Example 1, listed in Table 1B, the following flux results listed in Table 1C below were obtained:

TABLE 1C

Hours	$\mu g/cm^2/hr$					
	Test 1-1	Test 1-2	Test 1-3	Test 1-4	Average of all 4 tests	Std Dev
5	3.322	2.589	3.606	3.090	3.152	0.431
20	6.782	5.884	6.417	5.619	6.175	0.523
24	7.303	6.335	6.814	6.002	6.613	0.568
29	7.503	6.517	7.003	6.177	6.800	0.578
44	7.956	6.675	7.184	6.502	7.079	0.652
48	8.158	6.773	7.288	6.651	7.218	0.685
53	8.225	6.777	7.289	6.696	7.247	0.703
68	8.255	6.718	7.253	6.807	7.258	0.704
72	8.335	6.738	7.286	6.883	7.311	0.721
77	8.350	6.699	7.261	6.901	7.303	0.736
94	8.270	6.541	7.116	6.885	7.203	0.749
120	8.258	6.412	6.980	6.970	7.155	0.782
144	8.270	6.311	6.844	6.912	7.084	0.835
168	8.247	6.203	6.695	6.819	6.991	0.879
F_{5-168}	**8.438**	**6.303**	**6.825**	**7.044**	**7.152**	**0.912**
CORR	**1.000**	**0.998**	**0.998**	**1.000**	**0.999**	

EXAMPLE 2

A Felodipine reservoir and adhesive formulation was prepared having the formulation set forth in Table 2A below:

TABLE 2A

Ingredient	Amount (gm)
Felodipine	0.35
Ethanol	22.0 (95%)
Water	27.0
Total	49.35
Polyethylene membrane	
Silicone adhesive	

The formulation of Example 2 was prepared and incorporated into a permeation testing apparatus according to the same procedure as in Example 1.

The formulation of Example 2 was tested as in Example 1. Sample size and HPLC conditions were the same as in Example 1. Three replicate tests were conducted as in Example 1 (2-1, 2-2, 2-3) giving the results listed in Table 2B below:

TABLE 2B

	$\mu g/cm^2$				
Hours	**Test 2-1**	**Test 2-2**	**Test 2-3**	**Average of all 3 tests**	**Std Dev**
6	146.891	107.042	128.790	127.574	19.952
24	318.265	254.631	298.089	290.328	32.519
30	356.152	285.942	334.140	325.411	35.910
48	419.283	340.057	390.594	383.311	40.112
54	441.157	359.774	410.041	403.657	41.065
72	490.563	410.714	457.479	452.919	40.119
78	509.280	429.123	475.152	471.185	40.225
96	555.008	474.763	519.868	516.546	40.225
102	572.311	491.097	538.296	533.901	40.785
120	618.214	533.222	582.911	578.116	42.698
144	686.036	591.927	641.327	639.763	47.074
168	749.047	645.200	693.499	695.915	51.956

Based on the permeation results of Example 2, listed in Table 2B, the following flux results listed in Table 2C below were obtained:

TABLE 2C

Hours	$\mu g/cm^2/hr$				
	Test 2-1	**Test 2-2**	**Test 2-3**	**Average of all 3 tests**	**STD DEV**
6	24.482	17.840	21.465	21.262	3.325
24	13.261	10.610	12.420	12.097	1.355
30	11.872	9.531	11.138	10.847	1.197
48	8.735	7.085	8.137	7.986	0.836
54	8.170	6.662	7.593	7.475	0.760
72	6.813	5.704	6.354	6.291	0.557
78	6.529	5.502	6.092	6.041	0.516
96	5.781	4.945	5.415	5.381	0.419
102	5.611	4.815	5.277	5.234	0.400
120	5.152	4.444	4.858	4.818	0.356
144	4.764	4.111	4.454	4.443	0.327
168	4.459	3.840	4.128	4.142	0.309
F_{6-168}	3.273	2.993	3.072	3.113	0.144
CORR	0.973	0.978	0.970	0.974	
F_{48-168}	2.721	2.536	2.533	2.597	0.107

EXAMPLE 3 (38)

A Felodipine reservoir and adhesive formulation was prepared having the formulation set forth in Table 3A below:

TABLE 3A

Ingredient	Amount (gm)
Felodipine	0.35
Ethanol	22.0 (95%)
Water	27.0
Total	49.35
Polyethylene membrane	
Silicone adhesive	

The formulation of Example 3 was prepared and incorporated into a permeation testing apparatus according to the same procedure as in Example 1.

The formulation of Example 3 was tested as in Example 1. Sample size and HPLC conditions were the same as in Example 1. Three replicate tests were conducted as in Example 1 (3-1, 3-2, 3-3) giving the results listed in Table 3B below:

TABLE 3B

	$\mu g/cm^2$				
Hours	**Test 3-1**	**Test 3-2**	**Test 3-3**	**Average of all 3 tests**	**Std Dev**
6	169.393	137.617	171.512	159.507	18.987
24	479.007	366.231	465.646	443.628	50.154
30	554.838	447.557	537.259	513.218	57.539
48	673.637	557.190	644.156	624.994	60.542
54	710.424	589.928	673.732	658.028	61.764
72	775.731	658.875	730.494	721.700	58.922
78	797.630	683.131	750.651	743.804	57.556
96	849.997	740.000	798.214	796.070	55.030
102	869.626	760.343	816.749	815.573	54.651
120	920.773	815.518	863.640	866.644	52.692
144	989.349	893.304	927.645	936.766	48.668
168	1051.437	959.128	984.684	998.416	47.652

Based on the permeation results of Example 3, listed in Table 3B, the following flux results listed in Table 3C below were obtained:

TABLE 3C

Hours	µg /cm²/hr				
	Test 3-1	Test 3-2	Test 3-3	Average of all 3 tests	STD DEV
6	28.232	22.936	28.585	26.585	3.165
24	19.959	16.093	19.402	18.485	2.090
30	18.495	14.919	17.909	17.107	1.918
48	14.034	11.608	13.420	13.021	1.261
54	13.156	10.925	12.477	12.186	1.144
72	10.774	9.151	10.146	10.024	0.818
78	10.226	8.758	9.624	9.536	0.738
96	8.854	7.708	8.315	8.292	0.573
102	8.526	7.454	8.007	7.996	0.536
120	7.673	6.796	7.197	7.222	0.439
144	6.870	6.204	6.442	6.505	0.338
168	6.259	5.709	5.861	5.943	0.284
F_{6-168}	4.577	4.447	4.171	4.398	0.208
CORR	0.927	0.955	0.924	0.936	
F_{48-168}	3.076	3.309	2.794	3.060	0.258

EXAMPLE 4

A Felodipine reservoir and adhesive formulation was prepared having the formulation set forth in Table 4A below:

TABLE 4A

Ingredient	Amount (gm)
Felodipine	0.17
Ethanol	10.93 (95%)
Water	13.4
Klucel HF (enhancer/gelling agent)	0.50
Total	25.0
Polyethylene membrane	
Silicone adhesive	

The formulation of Example 4 was prepared and incorporated into a permeation testing apparatus according to the same procedure as in Example 1, using Klucel HF as a gelling agent/enhancer.

The formulation of Example 4 was tested as in Example 1. Sample size and HPLC conditions were the same as in Example 1. Three replicate tests were conducted as in Example 1 (4-1, 4-2, 4-3) were conducted giving the results listed in Table 4B below:

TABLE 4B

	$\mu g/cm^2$				
Hours	**Test 4-1**	**Test 4-1**	**Test 4-3**	**Average of all 3 tests**	**Std Dev**
6	40.368	63.676	97.437	67.160	28.694
24	132.406	165.607	235.124	177.712	52.418
30	143.927	188.622	252.759	195.103	54.705
48	185.019	249.691	310.949	248.553	62.973
54	196.244	272.670	323.827	264.247	64.207
72	232.750	325.489	382.304	313.514	75.493
78	241.331	338.190	391.950	323.824	76.330
96	278.900	387.065	444.166	370.044	83.938
120	337.993	463.965	528.622	443.527	96.944
144	403.941	535.572	612.357	517.290	105.404
168	420.701	590.410	672.512	561.208	128.420

Based on the permeation results of Example 10, listed in Table 10B, the following flux results listed in Table 10C below were obtained:

TABLE 4C

Hours	μg/cm²/hr				
	Test 4-1	Test 4-2	Test 4-3	Average of all 3 tests	STD DEV
6	6.728	10.613	16.240	11.193	4.782
24	5.517	6.900	9.797	7.405	2.184
30	4.798	6.287	8.425	6.503	1.823
48	3.855	5.202	6.478	5.178	1.312
54	3.634	5.049	5.997	4.893	1.189
72	3.233	4.521	5.310	4.354	1.049
78	3.094	4.336	5.025	4.152	0.979
96	2.905	4.032	4.627	3.855	0.874
120	2.817	3.866	4.405	3.696	0.808
144	2.805	3.719	4.252	3.592	0.732
168	2.504	3.514	4.003	3.341	0.764
F_{6-168}	2.247	3.111	3.286	2.882	0.556
CORR	0.990	0.994	0.991	0.993	
F_{48-168}	2.097	2.864	3.092	2.685	0.521

EXAMPLE 5

A Felodipine reservoir and adhesive formulation was prepared having the formulation set forth in Table 5A below:

TABLE 5A

Ingredient	Amount (gm)
Felodipine	0.17
Ethanol	10.93 (95%)
Water	13.4
Klucel HF (enhancer/gelling agent)	0.50
Total	25.0
Polyethylene membrane	
Silicone adhesive	

The formulation of Example 5 was prepared and incorporated into a permeation testing apparatus according to the same procedure as in Example 1.

The formulation of Example 5 was tested as in Example 1. Sample size and HPLC conditions were the same as in Example 1. Three replicate tests were conducted as in Example 1 (5-1, 5-2, 5-3) were conducted giving the results listed in Table 5B below:

TABLE 5B

	$\mu g/cm^2$				
Hours	**Test 5-1**	**Test 5-2**	**Test 5-3**	**Average of all 3 tests**	**Std Dev**
6	108.929	102.945	78.883	96.920	15.904
24	313.118	279.095	234.543	275.585	39.405
30	348.029	308.172	262.911	306.371	42.588
48	447.447	417.596	349.656	404.900	50.117
54	469.616	458.469	386.127	438.071	45.328
72	552.474	549.480	449.686	517.213	58.500
78	569.641	557.283	459.007	528.644	60.623
96	641.635	631.581	523.665	598.960	65.401
120	727.598	722.084	609.134	686.272	66.860
144	790.178	801.927	685.602	759.236	64.039
168	828.213	865.658	752.954	815.608	57.400

Based on the permeation results of Example 5, listed in Table 5B, the following flux results listed in Table 5C below were obtained:

TABLE 5C

Hours	$\mu g/cm^2/hr$				
	Test 5-1	**Test 5-2**	**Test 5-3**	**Average of all 3 tests**	**STD DEV**
6	18.155	17.158	13.147	16.153	2.651
24	13.047	11.629	9.773	11.483	1.642
30	11.601	10.272	8.764	10.212	1.420
48	9.322	8.700	7.285	8.435	1.044
54	8.697	8.490	7.151	8.112	0.839
72	7.673	7.632	6.246	7.184	0.812
78	7.303	7.145	5.885	6.777	0.777
96	6.684	6.579	5.455	6.239	0.681
120	6.063	6.017	5.076	5.719	0.557
144	5.487	5.569	4.761	5.272	0.445
168	4.930	5.153	4.482	4.855	0.342
$F_{6\text{-}168}$	4.117	4.455	3.876	4.149	0.291
CORR	0.968	0.961	0.985	0.979	
$F_{48\text{-}168}$	3.286	3.698	3.332	3.439	0.226

EXAMPLE 6

A Felodipine active drug/adhesive matrix formulation was prepared having the formulation set forth in Table 6A below:

TABLE 6A

Ingredient	Amount (gm)
Felodipine	0.4
Ethyl acetate	1.6
BIO PSA 7-4302 (adhesive solution) containing 9.6 gm silicone adhesive (60% solids)	16
Total	18

The formulation of Table 6A was prepared and incorporated into a permeation testing apparatus according to the following procedure:

1. Felodipine is dispersed in the requisite amount of ethyl acetate and adhesive solution to make the active drug/adhesive matrix.
2. The active drug/adhesive matrix is applied to a backing layer and dried.
3. The formulation is then applied to the human cadaver skin affixed to the receptor cell.

The formulation of Example 6 was tested using a permeation cell with a definable surface area for permeation. The receptor of the permeation cell was Ethanol:water (40:60) and the test substrate through which transdermal delivery was sought was human cadaver skin. Samples of 1.0 ml were taken at time intervals set out in Table 6B. These samples were tested for felodipine concentration using high performance liquid chromatography (HPLC). The HPLC conditions for determination of drug concentration are set forth below:

HPLC conditions for determination of felodipine concentration.

Column	Hypersil C18, 5μm, 4.6mm x 25cm
Mobile phase	Acetonitrile/Buffer 70/30
Buffer:	0.01M phosphate @ pH 4.5
Flow rate	1 ml/min

UV detection	237 nm
Injection volume	20 microl
Retention time	5.0 min

Three replicate tests (6-1, 6-2, 6-3) were conducted giving the results listed in Table 6B below:

TABLE 6B

Test #	Sampling Time (Hours)	Drug Conc. (μg/ml)	Receptor Volume (ml)	Drug Amount (μg)	Sampling Volume (ml)	Drug Loss due to Sampling (μg)	Cumulative Drug Loss (μg)	Cumulative Amount Permeated (μg)	Amount Permeated per cm^2 (μg/cm^2)
6-1	4	1.239	13	16.107	1	1.239	0.000	16.107	9.115
	24	17.305	13	224.965	1	17.305	1.239	226.204	128.016
	28	18.888	13	245.544	1	18.888	18.544	264.088	149.456
	48	31.875	13	414.375	1	31.875	37.432	451.807	255.692
	52	31.676	13	411.788	1	31.676	69.307	481.095	272.267
	72	42.285	13	549.705	1	42.285	100.983	650.688	368.244
	76	40.663	13	528.619	1	40.663	143.268	671.887	380.242
	96	49.885	13	648.505	1	49.885	183.931	832.436	471.101
6-2	4	1.496	13	19.448	1	1.496	0.000	19.448	11.006
	24	17.102	13	222.326	1	17.102	1.496	223.822	126.668
	28	18.597	13	241.761	1	18.597	18.598	260.359	147.345
	48	30.864	13	401.232	1	30.864	37.195	438.427	248.119
	52	30.158	13	392.054	1	30.158	68.059	460.113	260.392
	72	39.394	13	512.122	1	39.394	98.217	610.339	345.410
	76	37.508	13	487.604	1	37.508	137.611	625.215	353.829
	96	45.719	13	594.347	1	45.719	175.119	769.466	435.465
6-3	4	1.649	13	21.437	1	1.649	0.000	21.437	12.132
	24	17.004	13	221.052	1	17.004	1.649	222.701	126.033
	28	18.247	13	237.211	1	18.247	18.653	255.864	144.801
	48	30.048	13	390.624	1	30.048	36.900	427.524	241.949
	52	30.057	13	390.741	1	30.057	66.948	457.689	259.020
	72	39.708	13	516.204	1	39.708	97.005	613.209	347.034
	76	38.521	13	500.773	1	38.521	136.713	637.486	360.773
	96	46.559	13	605.267	1	46.559	175.234	780.501	441.710

Based on the permeation results of Example 6, listed in Table 6B, the averages of all three tests were calculated and the flux results listed in Table 6C below were obtained:

TABLE 6C

	μg/cm^2					
Hours	**6-1**	**6-2**	**6-3**	**Average of all 3 tests**	**Std Dev**	**μg/cm2/hr**
4	9.115	11.006	12.132	10.751	1.525	2.688
24	128.016	126.668	126.033	126.906	1.013	5.288
28	149.456	147.345	144.801	147.201	2.331	5.257
48	255.692	248.119	241.949	248.587	6.883	5.179
52	272.267	260.392	259.020	263.893	7.284	5.075
72	368.244	345.410	347.034	353.563	12.740	4.911
76	380.242	353.829	360.773	364.948	13.693	4.802
96	471.101	435.465	441.710	449.425	19.030	4.682
F_{4-96}	**4.978**	**4.545**	**4.626**	**4.716**	**0.230**	
CORR	**0.998**	**0.996**	**0.998**	**0.997**		

EXAMPLE 7

A Felodipine active drug/adhesive matrix formulation was prepared having the formulation set forth in Table 7A below:

TABLE 7A

Ingredient	Amount (gm)
Felodipine	0.23
Ethyl acetate	0.89
BIO PSA 7-4302 (adhesive solution) containing 12.4 gm silicone adhesive (60% solids)	20.6
Total	21.72

The formulation of Example 7 was prepared and incorporated into a permeation testing apparatus according to the same procedure as in Example 6.

The formulation of Example 7 was tested as in Example 6. Sample size and HPLC conditions were the same as in Example 6. Three replicate tests were conducted as in Example 1 (7-1, 7-2, 7-3) giving the results listed in Table 7B below:

TABLE 7B

	$\mu g/cm^2$				
Hours	**Test 7-1**	**Test 7-2**	**Test 7-3**	**Average of all 3 tests**	**Std Dev**
4	26.875	19.504	21.409	22.596	3.826
24	209.015	157.684	169.624	178.774	26.861
28	241.274	173.509	189.550	201.444	35.414
48	326.658	260.359	280.237	289.085	34.024
52	356.100	276.127	295.224	309.150	41.766
72	405.952	326.666	342.315	358.311	41.994
76	424.112	343.125	357.132	374.790	43.285
96	454.743	376.769	382.102	404.538	43.560
120	514.126	444.969	445.265	468.120	39.843
144	545.256	491.092	476.237	504.195	36.327
168	570.977	526.639	502.035	533.217	34.939

Based on the permeation results of Example 7, listed in Table 7B, the averages of all three tests were calculated and the flux results listed in Table 7C below were obtained:

TABLE 7C

	$\mu g/cm^2/hr$				
Hours	**Test 7-1**	**Test 7-2**	**Test 7-3**	**Average of all 3 tests**	**STD DEV**
4	6.719	4.876	5.352	5.649	0.957
24	8.709	6.570	7.068	7.449	1.119
28	8.617	6.197	6.770	7.194	1.265
48	6.805	5.424	5.838	6.023	0.709
52	6.848	5.310	5.677	5.945	0.803
72	5.638	4.537	4.754	4.977	0.583
76	5.580	4.515	4.699	4.931	0.570
96	4.737	3.925	3.980	4.214	0.454
120	4.284	3.708	3.711	3.901	0.332
144	3.787	3.410	3.307	3.501	0.252
168	3.399	3.135	2.988	3.174	0.208
F_{4-168}	**2.931**	**2.854**	**2.642**	**2.809**	**0.150**
CORR	**0.934**	**0.970**	**0.948**	**0.952**	

EXAMPLE 8

A Felodipine active drug/adhesive matrix formulation was prepared having the formulation set forth in Table 8A below:

TABLE 8A

Ingredient	Amount (gm)
Felodipine	0.46
Ethyl acetate	1.78
BIO PSA 7-4302 (adhesive solution) containing 11.5 gm silicone adhesive (60% solids)	19.2
Total	21.44

The formulation of Example 8 was prepared and incorporated into a permeation testing apparatus according to the same procedure as in Example 6.

The formulation of Example 8 was tested as in Example 6. Sample size and HPLC conditions were the same as in Example 6. Three replicate tests were conducted as in Example 6 (8-1, 8-2, 8-3) giving the results listed in Table 8B below:

TABLE 8B

	$\mu g/cm^2$				
Hours	**Test 8-1**	**Test 8-2**	**Test 8-3**	**Average of all 3 tests**	**Std Dev**
4	18.349	23.374	47.954	29.892	15.842
24	192.718	207.370	308.729	236.272	63.176
28	225.636	232.085	335.990	264.570	61.935
48	325.358	345.351	487.377	386.029	88.338
52	346.537	374.671	517.759	412.989	91.817
72	404.506	434.863	599.225	479.531	104.763
76	418.675	456.259	620.123	498.352	107.118
96	459.932	499.242	653.037	537.404	102.052
120	537.091	560.783	730.431	609.435	105.453
144	584.445	602.545	777.568	654.853	106.659
168	624.448	641.538	811.649	692.545	103.500

Based on the permeation results of Example 8, listed in Table 8B, the averages of all three tests were calculated and the flux results listed in Table 8C below were obtained:

TABLE 8C

Hours	$\mu g/cm^2/hr$				
	Test 8-1	**Test 8-2**	**Test 8-3**	**Average of all 3 tests**	**STD DEV**
4	4.587	5.844	11.989	7.473	3.961
24	8.030	8.640	12.864	9.845	2.632
28	8.058	8.289	12.000	9.449	2.212
48	6.778	7.195	10.154	8.042	1.840
52	6.664	7.205	9.957	7.942	1.766
72	5.618	6.040	8.323	6.660	1.455
76	5.509	6.003	8.160	6.557	1.409
96	4.791	5.200	6.802	5.598	1.063
120	4.476	4.673	6.087	5.079	0.879
144	4.059	4.184	5.400	4.548	0.741
168	3.717	3.819	4.831	4.122	0.616
F_{4-168}	**3.346**	**3.417**	**4.105**	**3.623**	**0.419**
CORR	**0.959**	**0.949**	**0.927**	**0.944**	

EXAMPLE 9

A Felodipine active drug/adhesive matrix formulation was prepared having the formulation set forth in Table 9A below:

TABLE 9A

Ingredient	Amount (gm)
Felodipine	0.70
Ethyl acetate	2.67
BIO PSA 7-4302 (adhesive solution) containing 10.7 gm silicone adhesive (60% solids)	17.8
Total	21.17

The formulation of Example 9 was prepared and incorporated into a permeation testing apparatus according to the same procedure as in Example 6.

The formulation of Example 9 was tested as in Example 6. Sample size and HPLC conditions were the same as in Example 6. Three replicate tests were conducted as in Example 6 (9-1, 9-2, 9-3) giving the results listed in Table 9B below:

TABLE 9B

	$\mu g/cm^2$				
Hours	**Test 9-1**	**Test 9-2**	**Test 9-3**	**Average of all 3 tests**	**Std Dev**
4	16.524	37.455	36.918	30.299	11.933
24	205.379	314.447	301.913	273.913	59.682
28	232.196	356.446	338.405	309.016	67.137
48	337.964	479.965	484.818	434.249	83.421
52	362.508	525.171	529.111	472.263	95.071
72	415.780	600.848	613.187	543.272	110.583
76	430.774	633.583	667.014	577.124	127.840
96	468.083	673.445	704.399	615.309	128.437
120	549.756	778.694	806.885	711.778	141.022
144	609.880	840.617	884.202	778.233	147.418
168	659.291	902.965	939.035	833.764	152.170

Based on the permeation results of Example 9, listed in Table 9B, the averages of all three tests were calculated and the flux results listed in Table 9C below were obtained:

TABLE 9C

Hours	µg/cm²/hr				
	Test 9-1	**Test 9-2**	**Test 9-3**	**Average of all 3 tests**	**STD DEV**
4	4.131	9.364	9.230	7.575	2.983
24	8.557	13.102	12.580	11.413	2.487
28	8.293	12.730	12.086	11.036	2.398
48	7.041	9.999	10.100	9.047	1.738
52	6.971	10.099	10.175	9.082	1.828
72	5.775	8.345	8.516	7.545	1.536
76	5.668	8.337	8.777	7.594	1.682
96	4.876	7.015	7.337	6.409	1.338
120	4.581	6.489	6.724	5.931	1.175
144	4.235	5.838	6.140	5.404	1.024
168	3.924	5.375	5.589	4.963	0.906
F_{4-168}	**3.497**	**4.653**	**5.004**	**4.385**	**0.789**
CORR	**0.962**	**0.951**	**0.956**	**0.956**	

EXAMPLE 10 (42)

A Felodipine active drug/adhesive matrix formulation was prepared having the formulation set forth in Table 10A below:

TABLE 10A

Ingredient	Amount (gm)
Felodipine	0.4
Ethyl acetate	1.5
BIO PSA 7-4302 (adhesive solution) containing 18.6 gm silicone adhesive (60% solids)	31.0
Total	32.9

The formulation of Example 10 was prepared and incorporated into a permeation testing apparatus according to the same procedure as in Example 6.

The formulation of Example 10 was tested as in Example 6. Sample size and HPLC conditions were the same as in Example 6. Three replicate tests were conducted as in Example 6 (10-1, 10-2, 10-3) giving the results listed in Table 10B below:

TABLE 10B

	$\mu g/cm^2$				
Hours	**Test 10-1**	**Test 10-2**	**Test 10-3**	**Average of all 3 tests**	**Std Dev**
6	40.068	76.197	35.599	50.621	22.262
24	251.407	331.110	241.432	274.650	49.150
30	293.227	380.646	279.694	317.856	54.797
48	376.524	470.580	355.225	400.776	61.383
54	405.810	501.570	388.094	431.825	61.047
72	459.156	568.308	439.166	488.883	69.505
78	479.973	592.938	463.962	512.291	70.300
96	525.231	642.425	504.857	557.504	74.246
102	540.975	667.262	521.104	576.447	79.273
120	574.084	698.860	550.553	607.832	79.705
144	612.784	744.643	584.507	647.311	85.469
168	657.051	798.065	631.916	695.677	89.557

Based on the permeation results of Example 10, listed in Table 10B, the averages of all three tests were calculated and the flux results listed in Table 10C below were obtained:

TABLE 10C

Hours	$\mu g/cm^2/hr$				
	Test 10-1	Test 10-2	Test 10-3	Average of all 3 tests	STD DEV
6	6.678	12.700	5.933	8.437	3.710
24	10.475	13.796	10.060	11.444	2.048
30	9.774	12.688	9.323	10.595	1.827
48	7.844	9.804	7.401	8.350	1.279
54	7.515	9.288	7.187	7.997	1.131
72	6.377	7.893	6.100	6.790	0.965
78	6.154	7.602	5.948	6.568	0.901
96	5.471	6.692	5.259	5.807	0.773
102	5.304	6.542	5.109	5.651	0.777
120	4.784	5.824	4.588	5.065	0.664
144	4.255	5.171	4.059	4.495	0.594
168	3.911	4.750	3.761	4.141	0.533
F_{6-168}	3.299	3.827	3.183	3.436	0.343
CORR	0.935	0.933	0.935	0.935	

EXAMPLE 11

A Felodipine active drug/adhesive matrix formulation was prepared having the formulation set forth in Table 11A below:

TABLE 11A

Ingredient	Amount (gm)
Felodipine	0.4
Ethyl acetate	1.5
BIO PSA 7-4302 (adhesive solution) containing 18.6 gm silicone adhesive (60% solids)	31.0
Total	32.9

The formulation of Example 11 was prepared and incorporated into a permeation testing apparatus according to the same procedure as in Example 6.

The formulation of Example 11 was tested as in Example 6. Sample size and HPLC conditions were the same as in Example 6. Three replicate tests were conducted as in Example 6 (11-1, 11-2, 11-3) giving the results listed in Table 11B below:

TABLE 11B

	$\mu g/cm^2$				
Hours	**Test 11-1**	**Test 11-2**	**Test 11-3**	**Average of all 3 tests**	**Std Dev**
6	68.937	58.295	70.662	65.965	6.698
24	263.402	269.001	290.024	274.142	14.036
30	295.223	307.997	322.300	308.507	13.546
48	352.382	370.535	377.866	366.928	13.119
54	378.195	391.252	392.165	387.204	7.815
72	423.208	431.628	432.850	429.229	5.250
78	443.895	448.411	452.170	448.159	4.143
96	480.775	476.123	486.720	481.206	5.312
102	497.597	488.703	493.466	493.255	4.451
120	528.767	511.241	524.125	521.378	9.080
144	568.225	537.408	554.291	553.308	15.432
168	626.550	576.344	603.543	602.146	25.132

Based on the permeation results of Example 11, listed in Table 11B, the averages of all three tests were calculated and the flux results listed in Table 11C below were obtained:

TABLE 11C

Hours	μg/cm²/hr				
	Test 11-1	Test 11-2	Test 11-3	Average of all 3 tests	STD DEV
6	11.490	9.716	11.777	10.994	1.116
24	10.975	11.208	12.084	11.423	0.585
30	9.841	10.267	10.743	10.284	0.452
48	7.341	7.719	7.872	7.644	0.273
54	7.004	7.245	7.262	7.170	0.145
72	5.878	5.995	6.012	5.962	0.073
78	5.691	5.749	5.797	5.746	0.053
96	5.008	4.960	5.070	5.013	0.055
102	4.878	4.791	4.838	4.836	0.044
120	4.406	4.260	4.368	4.345	0.076
144	3.946	3.732	3.849	3.842	0.107
168	3.729	3.431	3.593	3.584	0.150
$F_{6\text{-}168}$	2.911	2.592	2.643	2.715	0.171
CORR	0.947	0.904	0.917	0.925	

EXAMPLE 12

A Felodipine active drug/adhesive matrix formulation was prepared having the formulation set forth in Table 12A below:

TABLE 12A

Ingredient	Amount (gm)
Felodipine	0.4
Ethyl acetate	1.6
DURO-TAK 87-4098 (adhesive solution) containing 9.6 gm acrylate adhesive (38.5% solids)	24.0
Total	26.0

The formulation of Example 12 was prepared and incorporated into a permeation testing apparatus according to the same procedure as in Example 6.

Three permeation tests (12-1, 12-2, 12-3) were conducted giving the results listed in Table 12B below:

TABLE 12B

Test #	Sampling Time (Hours)	Drug Conc. (μg/ml)	Receptor Volume (ml)	Drug Amount (μg)	Sampling Volume (ml)	Drug Loss due to Sampling (μg)	Cumulative Drug Loss (μg)	Cumulative Amount Permeated (μg)	Amount Permeated per cm^2 (μg/cm^2)
12-1	4	0.000	13	0	1	0.000	0.000	0.000	0.000
	24	3.233	13	42.029	1	3.233	0.000	42.029	23.786
	28	3.623	13	47.099	1	3.623	3.233	50.332	28.484
	48	6.601	13	85.813	1	6.601	6.856	92.669	52.444
	52	6.694	13	87.022	1	6.694	13.457	100.479	56.864
	72	9.825	13	127.725	1	9.825	20.151	147.876	83.688
	76	9.631	13	125.203	1	9.631	29.976	155.179	87.821
	96	12.587	13	163.631	1	12.587	39.607	203.238	115.019
12-2	4	0.000	13	0	1	0.000	0.000	0.000	0.000
	24	2.486	13	32.318	1	0.000	0.000	32.318	18.290
	28	2.775	13	36.075	1	2.486	2.486	38.561	21.823
	48	5.056	13	65.728	1	5.261	5.261	70.989	40.175
	52	5.152	13	66.976	1	10.317	10.317	77.293	43.743
	72	7.270	13	94.51	1	15.469	15.469	109.979	62.241
	76	7.171	13	93.223	1	22.739	22.739	115.962	65.626
	96	8.958	13	116.454	1	29.910	29.910	146.364	82.832
12-3	4	0.000	13	0	1	0.000	0.000	0.000	0.000
	24	3.603	13	46.839	1	0.000	0.000	46.839	26.508
	28	4.013	13	52.169	1	.3603	3.603	55.772	31.563
	48	7.395	13	96.135	1	7.616	7.616	103.751	58.716
	52	7.389	13	96.057	1	15.011	15.011	111.068	62.857
	72	10.193	13	132.509	1	22.400	22.400	154.909	87.668
	76	9.894	13	128.622	1	32.593	32.593	161.215	91.237
	96	12.507	13	162.591	1	42.487	42.487	205.078	116.060

Based on the permeation results of Example 12, listed in Table 12B, the averages of the three tests were calculated and the permeation results and mean flux rates between 4-96 hours ($F_{4\text{-}96}$) are listed in Table 12C below:

TABLE 12C

Hours	μg/cm²				
	Test 12-1	Test 12-2	Test 12-3	Average of all 3 tests	STD DEV
4	0.000	0.000	0.000	0.000	0.000
24	23.786	18.290	26.508	22.861	4.186
28	28.484	21.823	31.563	27.290	4.979
48	52.444	40.175	58.716	50.445	9.431
52	56.864	43.743	62.857	54.488	9.776
72	83.688	62.241	87.668	77.866	13.677
76	87.821	65.626	91.237	81.561	13.906
96	115.019	82.832	116.060	104.637	18.891
F_{4-96}	**1.247**	**0.905**	**1.260**	**1.137**	**0.201**
CORR	**1.000**	**1.000**	**1.000**	**1.000**	

EXAMPLE 13

A Felodipine double active drug/adhesive matrix and membrane formulation was prepared having the formulation set forth in Table 13A below:

TABLE 13A

Ingredient	Amount (gm)
MATRIX 1	
Felodipine	0.93
Ethyl acetate	3.56
BIO PSA 7-4302 (adhesive solution) containing 10.6 gm silicone adhesive (60% solids)	18.1
Total	22.59
Polyethylene membrane	
MATRIX 2	
Felodipine	0.23
Ethyl acetate	0.89
BIO PSA 7-4302 (adhesive solution) containing 12.4 gm silicone adhesive (60% solids)	20.6
Total	21.72

The formulation of Example 13 was prepared and incorporated into a permeation testing apparatus according to the following procedure:

1. For each matrix layer, felodipine is mixed with the requisite amounts of ethyl acetate and adhesive solution to form the active drug/adhesive matrix.
2. Matrix formulation 1 is applied to the first side of the polyethylene membrane and matrix formulation 2 is applied to the opposite side of the membrane.
3. The formulation is then applied to the human cadaver skin affixed to the receptor cell.

The formulation of Example 13 was tested as in Example 6. Sample size and HPLC conditions were the same as in Example 6. Three replicate tests were conducted as in Example 1 (13-1, 13-2, 13-3) giving the results listed in Table 13B below:

TABLE 13B

	$\mu g/cm^2$				
Hours	**Test 13-1**	**Test 13-2**	**Test 13-3**	**Average of all 3 tests**	**Std Dev**
6	15.053	18.165	8.233	13.817	5.080
24	123.668	110.952	100.638	111.753	11.536
30	140.464	127.509	118.565	128.846	11.011
48	178.559	161.833	158.357	166.250	10.801
54	188.593	170.394	168.737	175.908	11.017
72	224.920	196.713	204.042	208.558	14.636
78	234.522	205.007	212.800	217.443	15.295
96	270.577	231.195	246.148	249.307	19.880
102	280.244	236.690	252.634	256.523	22.036
120	320.146	267.732	284.959	290.946	26.715
168	402.896	329.425	359.332	363.884	36.946

Based on the permeation results of Example 13, listed in Table 13B, the following flux results listed in Table 13C below were obtained:

TABLE 13C

Hours	µg/cm²/hr				
	Test 13-1	Test 13-2	Test 13-3	Average of all 3 tests	STD DEV
6	2.509	3.028	1.372	2.303	0.847
24	5.153	4.623	4.193	4.656	0.481
30	4.682	4.250	3.952	4.295	0.367
48	3.720	3.372	3.299	3.464	0.225
54	3.492	3.155	3.125	3.258	0.204
72	3.124	2.732	2.834	2.897	0.203
78	3.007	2.628	2.728	2.788	0.196
96	2.819	2.408	2.564	2.597	0.207
102	2.747	2.320	2.477	2.515	0.216
120	2.668	2.231	2.375	2.425	0.223
168	2.398	1.961	2.139	2.166	0.220
$F_{6\text{-}168}$	2.172	1.718	1.995	1.962	0.229
CORR	0.979	0.968	0.978	0.976	

It will be readily apparent that various modifications to the invention may be made by those skilled in the art without departing from the scope of this invention. For example, many different transdermal delivery systems may be utilized in order to obtain the relative release rates and plasma levels described herein. Further, it is possible that mean values for plasma concentrations over a particular patient population for a particular described time point along the dosing interval may vary from the plasma concentration ranges described herein for that time point. Such obvious modifications are considered to be within the scope of the appended claims.

In vitro skin permeation studies with cadaver skin quantitatively predict the pharmacokinetics and extent of drug absorption from the transdermal delivery dosage form. Matching in vitro skin donors to the in vivo population improves the correlation. Further improvements in this correlation are achieved by matching application sites.